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Process Development and Scale-up of Fully Synthetic Tetracycline TP-2758: A Potent Antibacterial Agent with Excellent Oral Bioavailability

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Synthesis of TP-2758

Significance: TP-2758 is in development for the treatment of complicated urinary tract infections caused by Gram-negative pathogens. The closing stage of the synthesis depicted features the installation of the chiral pyrrolidine moiety in fragment **G** using Ellman's chiral sulfinamine auxiliary **B** (99% ee). The conjunction of complex fragments **G** and **H** using chemistry developed by Myers and coworkers (*J. Am. Chem. Soc.* 2008, *130*, 17913) delivered the advanced intermediate **I** in 89% yield.

Comment: Enantioselective deprotonation of *N*-Boc pyrrolidine using *s*-BuLi and (–)-sparteine afforded the lithium reagent (*S*)-**K** that participated in a palladium-catalyzed Negishi coupling with bromoarene **J** to give enantioenriched pyrrolidine (*R*)-**L** in 63% yield (>90% ee). By using diamine (*S*,*S*)-**M** as a (+)-sparteine surrogate, the corresponding Negishi reaction delivered (*S*)-**L** in 50% yield (93% ee). Neither of these alternatives was robust, and the yields could not be improved.

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Synthesis of Natural Products and Potential Drugs

Key words

TP-2758

asymmetric deprotonation

Ellman-Davis asymmetric amine synthesis

Negishi reaction

palladium catalysis



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